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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/091,578	10/06/98	MADISON E	19191.0002

HM22/1112

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EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 11/12/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/091,578	Madison et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on *Aug 31, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-64* is/are pending in the applicat

Of the above, claim(s) *25-64* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *2 filed 09/21/98*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This application is a 371 U.S. National Stage filing of PCT/US99/20577, filed 12/19/96.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Sequences appear in the specification and claims, for example on page 34 of the specification at lines 25 and 27 and in claim 24.

Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification and the claims.

3. Applicant's election of the Invention of Group I (claims 1-24)and species of thrombolytic agent/anticoagulant as a therapeutic or diagnostic functional entity, a CDR of an immunoglobulin as a specific peptide mimetic source, and specific protein or specific polyamino acid and integrin as a specific target with traverse in Paper No. 9 filed 08/31/99 is acknowledged. Traversal is for the reasons of record. Applicant's arguments were considered, but not deemed persuasive for the reasons of record in Paper No. 7, mailed 06/30/99. In addition, failure of an examiner to make a lack of unity in a PCT application has no bearing on restriction as required under 35 U.S.C. 121 and 372 when it is determined that the 371 national stage application does not provide a technical feature that is distinguished over the prior art. The Groups lack unity of invention for the reasons of record and for the reasons enunciated in the art rejections in the instant Office Action, and therefore, only the elected Group I, claims 1-24, will be examined. Additionally in response to applicant's request to rejoin the claims of Groups V, VII, IX, X and XI with elected Group I because the former Groups are processes of using the product of Group I, process claims which depend from or otherwise include all the limitations of the allowed product claim may be rejoined after the product claim is found allowable (M.P.E.P. 821.04).

The invention being examined in this application is a targeted therapeutic or diagnostic agent comprising a thrombolytic agent/anticoagulant linked to a CDR of an immunoglobulin which specifically binds to integrin.

The requirement is still deemed proper and is therefore made FINAL.

Claims 25-64 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as

being drawn to a non-elected invention.

4. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 60/009, 028 filed 12/21/95. A reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included. Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

The first sentence of the specification should refer to the provisional application using language such as:
This application claims the benefit of U.S. Provisional Application No. 60/____, filed ____.
See MPEP 1302.04
If a statutory reference is included in this statement, if must be to 35 USC 119(e) and not to 35 USC 120.

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the declaration is defective in claiming priority to PCT/US96/20577 under 35 U.S.C. 119a-d. Priority claim should be made under 35 U.S.C. 120.

6. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al (J. Biol. Chem., Vol **270**, 1995, pages 30486-30490) as evidenced by Barbas et al (Proc. Natl. Acad. Sci. USA, Vol. 90, 1993, 10003-10007) and Gething et al (EMBO Journal, Vol. 7, 1988, pages 2731-2740).

Smith et al teach a targeted therapeutic or diagnostic agent comprising a therapeutic or diagnostic functional entity (human tPA) linked to an isolated, optimized, high-affinity

polyamino acid (the complementarity determining region, HCDR3, of antibody molecule Fab-9 optimized with an RGD sequence) that specifically binds a selected target (an integrin that binds to an RGD motif, specifically a β_3 integrin, $\alpha_{IIb}\beta_3$, which is a cell surface protein). Smith et al teach that the entity is LG-tPA (especially Materials and Methods section, line 17-18). Claim 21 is included because the RGD sequence binds β_3 integrins, including $\alpha_v\beta_3$ as evidenced by Barbas et al (especially Abstract). Claim 4 is included because the term "medical or diagnostic device" encompasses tPA, which can function in thrombolysis (especially page 30487, column 1, last sentence prior to Materials and Methods section of Smith et al). Claim 8 is included because tPA is an enzyme as evidenced by Gething et al (especially first sentence of Introduction section on page 2731). Claim 22 is included because the term "an IgG-like molecule" encompasses an IgG molecule. Claim 3 is included because the tPA is a protein comprising an isolated naturally occurring or optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein and replaces a surface loop on the protein, i.e., is protein loop grafted with HCDR3 of a monoclonal antibody that has been optimized with a sequence that binds β_3 integrins.

The reference teachings anticipate the claimed invention.

This rejection can be overcome by perfecting Applicant's priority claim under 35 U.S.C. 119(e), as in item #3 supra.

9. Claims 2, 4-13 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Paoni et al (Protein Eng., Vol. 6, 1993, pages 529-534) as evidenced by Gething et al (EMBO Journal, Vol. 7, 1988, pages 2731-2740).

Paoni et al teach a targeted therapeutic agent comprising a therapeutic functional entity (tPA) linked to an optimized, high-affinity polyamino acid (amino acid residues EIHPV of vampire bat tPA) that binds a selected target (fibrin) (especially page 533, column 1, last paragraph, and column 2). Paoni et al teach that the entity is loop-grafted tPA (especially page 533, column 1, last paragraph, and column 2). Claim 4 is included because the term "medical or diagnostic device" encompasses tPA, which can function in thrombolysis (especially page 533, last sentence and Introduction section, page 529). Claim 8 is included because tPA is an enzyme as evidenced by Gething et al (especially first sentence of Introduction section on page 2731).

The reference teachings anticipate the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art

are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bode et al (Circulation, Vol. 84, 1991, pages 805-813) in view of Barbas et al (Proc. Natl. Acad. Sci. Vol. 90, 1993, pages 10003-10007) and further in view of Todd et al (Clinical Diagnosis and Management by Laboratory Methods, 1979, Vol. 1, page 252), Johannessen et al (Thrombosis and Haemostasis, Vol. 63, 1990, pages 54-59) and Gordon et al (J. Med. Chem. Vol. 37, 1994, pages 1386-1401).

Bode et al teach a targeted therapeutic agent comprising a therapeutic functional entity (urokinase, a plasminogen activator) linked to a protein comprising an antibody (7E3, specific for platelet membrane glycoprotein IIb/IIIa) (especially Abstract and page 805). Bode et al also teach that arterial thrombi contain a high concentration of activated platelets, that platelets play a key role when initially reperfused vessels reocclude, and that combined administration of 7E3 and a thrombolytic agent reduces the rate of reocclusion and enhances the speed and efficacy of reperfusion in experimental animals (especially page 805, paragraph 1).

Bode et al do not teach that the therapeutic functional entity is linked to a protein which has undergone protein loop grafting, the nonendogenous loop binding a specific target. Bode et al do not teach that the therapeutic functional entity is linked to an optimized, high affinity polyamino acid that specifically binds a selected target. Bode et al do not teach the target is avb3 or aIIbb3 integrin that binds to an RGD motif.

Barbas et al teach Fab-9, an isolated, optimized, high-affinity polyamino acid (the complementarity determining region, HCDR3, of antibody molecule Fab-9 optimized with an RGD sequence) that specifically binds a selected target (an integrin that binds to an RGD motif, $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ (especially Figure 1 legend and Abstract). Barbas et al teach that integrin $\alpha_{IIb}\beta_3$ exacerbated an artherosclerotic lesion by enabling platelet adhesion and thrombus formation at the existing atherosclerotic plaque (especially page 10003, , column 2, lines 3-6) and teach design of anti-receptor antibodies, specifically for $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ by protein loop grafting of RGD (especially page 10004).

Todd et al teach that "plasminogen is the circulating proenzyme from which the fibrinolytic molecule, plasmin, is derived. The inactive protein can be converted to the enzymatically effective form by several endogenous activators found in many tissues, particularly within the vascular wall, and in the urinary tract, where the activator is specifically referred to as urokinase" (especially page 252, column 2, lines 1-9 of section entitled "Physiology").

Johannessen et al teach that tissue type plasminogen activator (t-PA) has a high throbolytic efficacy due to its high affinity for fibrin which results in a binding induced increase in activity as well as localization of the fibrinolytic activity to the site of the clot. Johannessen et al teach that fibrinolytic activity asociated with t-PA is accompanied by only modest systemic activation of plasmin and limited degradatin of plasma fibrinogen, and the desirability of producing an anologue with a long half-life in the circulation given the fact that t-PA is rapidly cleared from the bloodstream (especially Introduction section).

Gordon et al teach applications of combinatorial technologies to drug discovery.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the teaching of Bode of plasminogen activator linked to an antibody specific for a platelet membrane glycoprotein and because of the teaching of Barbas et al of Fab-9 and of the importance of platelet ahdesion in atherosclerotic plaques mediated by integrin $\alpha_{IIb}\beta_3$ and the teaching of Todd et al of the importance of plasminogen activators in fibrinolysis.

One of ordinary skill in the art at the time the invention was made would have been motivated to substitute for the 7E3 antibody in the invention of Bode et al another platelet specific antibody such as the Fab-9 antibody taught by Barbas et al, particularly in light of the teaching of Bode et al of a targeted therapeutic agent comprising a plasminogen activator and a platelet-specific antibody that acts to reduce the rate of reocclusion and enhance the speed and efficacy of reperfusion in experimental animals. One of ordinary skill in the art at the time the invention was made would also have been motivated to use an anti-platelet antibody specific for integrin $\alpha_{IIb}\beta_3$ such as Fab-9 particularly given the teaching of Barbas et al that integrin $\alpha_{IIb}\beta_3$ exacerbated an artherosclerotic lesion by enabling platelet adhesion and thrombus formation at the existing atherosclerotic plaque and the teaching of design of anti-receptor antibodies, specifically for $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ by protein loop grafting of RGD. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute another type of plasminogen activator such as tissue plasminogen activator for the plasminogen activator urokinase in the invention of Bode et al particularly in light of the teaching of Johannessen et al of the high efficacy and specificity of t-PA and the need for increasing the circulatory half-life of t-PA administered by itself. In addition, instant claim 1 is included because one of ordinary skill in the art at the time the invention was made would have been motivated to use an isolated peptide mimetic as taught by Gordon et al based on an optimized

high affinity polyamino acid as taught by Barbas et al and wherein the mimetic specifically binds a selected target.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because the usefulness of plasminogen activators linked to antibodies specific for platelets as taught by Bode et al was known in the art at the time the invention was made, the role of plasminogen activators in reducing thrombolysis and the role of platelets in thrombus formation and maintainance was known in the art as taught by Todd et al, Bode et al, Johannessen et al and Barbas et al, and monoclonal antibodies specific for platelet $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ integrins, such as Fab-9, were known in the art as taught by Barbas et al. Furthermore, protein loop grafting to create optimized high affinity polyamino acids was well known in the art and in specific, protein loop grafting involving the RGD integrin recognition sequence was also known. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.
Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Patent Examiner
Group 1640/Technology Center 1600
November 3, 1999

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